

To Study the Comparative Effect of Nebivolol and Metoprolol on Fasting and Post meal Blood Glucose Level in Patients of Type II Diabetes Mellitus with Essential Hypertension

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a metabolic disorder characterised by excessively high blood sugar levels and elevated oxidative stress, resulting in lipid, protein, and carbohydrate metabolism problems. Diabetes mellitus increases the risk of coronary artery disease, stroke, and other vascular problems considerably.

Aim: Nebivolol has enhanced tolerability profile with respect to adverse effects usually allied with nonselective β -blockers so, the study's goal is to assess the comparative effects of nebivolol and metoprolol on metabolic parameters in type II diabetes mellitus with essential hypertension patients.

Methodology: The subjects enrolled for this study are selected from the Out Patient Department of Medicine, MGM medical College, Aurangabad according to the inclusion and exclusion criteria. Written informed consent is obtained from each patient. Various biochemical parameters are assessed for comparative study of nebivolol and metoprolol drugs in patients. 3 month randomized open label study design is selected and 40 patients are divided into 2 groups, administered nebivolol and metoprolol in each group. Parameters like fasting blood glucose level, postprandial blood glucose level (BGL), HbA1c level, systolic and diastolic blood pressure are assessed using student paired and unpaired t-test.

Result: Fasting blood glucose level, postprandial BGL, HbA1c and systolic blood pressure except diastolic blood pressure are found to be reduced significant in nebivolol treated group than compared to metoprolol group patients. Nebivolol doesn't show side effect of fatigue.

Conclusion: This comparative study concluded that Nebivolol more efficacious than metoprolol in terms of reducing BGL, HbA1c and blood pressure along with lesser side effects in type II diabetic and hypertension patients.

Key Words: Nebivolol, Metoprolol, Fasting blood glucose level, Postprandial blood glucose level, HbA1c, Blood pressure

INTRODUCTION

Diabetes mellitus (DM) is a metabolic condition marked by high blood sugar levels and increased oxidative stress which leads to the altered metabolism of lipids, proteins and carbohydrates.¹ Diabetes mellitus further leads to risk of coronary heart disease, stroke and attribute to other vascular diseases.³ Cardiovascular risk is increased up to four times if the person is suffering simultaneously with hypertension and diabetes mellitus.^{2,4} Hypertension is usually widespread asymptomatic condition of elevated blood pressure which further become risk factor for the cardiovascular disease and leads to global mortality according to World Health Organization survey.⁵ Several antihypertensive regimens offered for

clinical management of hypertension but beta (β) blockers are efficiently used in clinical hypertension.⁶⁻⁹ non-selective beta-blockers have limited use in hypertensive patient with metabolic syndrome because they have negative impact on carbohydrate and lipid metabolism.¹⁰

Third-generation β -blockers are most suitable clinical therapeutic agents for metabolic disorders along with hypertension as they are providing better improvement in diabetes mellitus and reducing cardiovascular manifestation.^{11,12} Among Third-generation β -blockers, Nebivolol shown vasodilatory activity due to release of endothelial nitric oxide (NO) and become approved drug for the treatment of essential hypertension.¹³ Recently nitric oxide is

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noted for its engrossment for the in the directive for large arterial stiffness^{14,15} so arterial stiffening has hence know as a unique therapeutic target regarding blood pressure decrease and cardiovascular disease avoidance. Drugs such as nebivolol possibility decrease blood pressure and recover endothelial function could be expressly valuable particular and must be taken for granted as substitute first-line treatment for hypertension.

In addition, nebivolol enhances the bioavailability nitric oxide of endogenously.^{16,17} Nitric oxide further attenuations the PAI-1 expression¹⁸ and progresses sensitivity of insulin and uptake of glucose in muscle.¹⁹

Previous studies shown that nebivolol has enhanced tolerability profile, in response to adverse events usually related with nonselective β -blockers on cardiovascular, respiratory and metabolic functions.²⁰

Hence, by keeping above therapeutic action of nebivolol, research study was planned to evaluate the comparative effects of nebivolol with metoprolol on metabolic parameters with patients of essential hypertension concomitant type II diabetes mellitus.

METHODOLOGY

Patient selection

The current research was done in partnership with the Medicine Department in MGMs medical college and hospital Aurangabad. The subjects enrolled for this study were identified from the Out Patient Department of Medicine, MGM medical College, Aurangabad according to the inclusion and exclusion criteria. Written informed consent was obtained from each patient.

Study Design

12 week randomized open label single centre prospective clinical study. Patient desired to be a part of the study then his consent (signature or thumb impression) was taken in the informed consent form. The informed consent form was agreed by IRB/IERC. A Case Record Form was completed and signed by the investigator and complied according to ICH - GCP regulations. The study was carried out from 01/09/2011 to 30/11/2013. Patients were divided into two groups A and B. Group A 20 patients, received Metoprolol (50 mg twice daily). Group B also has 20 patients and received Nebivolol (5mg once daily) (Fig 1).

Study Parameters

After screening the eligibility of patients, the parameter were recorded in each patient like Physical examination, Systemic examination, Vital signs, Past medical history,

Concomitant medications, Clinical examination, Laboratory analysis. Study visits included clinic visits on day 0 and day 90. Patients underwent the same investigations during each visit. Biochemical tests like Fasting blood glucose level, post meal BGL, HbA1c and systolic and diastolic blood pressure were performed at day 0 and after 3 month treatment.

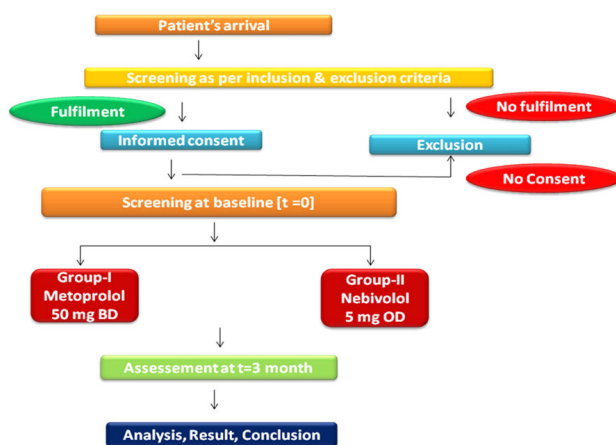


Figure 1: Flow chart of study.

Blood sugar and HbA1c assessment

Blood was drawn from patients via vein puncture, with all aseptic precautions taken. Fasting and Postprandial blood sugar assessment were done on semi auto analyzer by glucose oxidase /peroxidase [GOD / POD] method. Glucose is oxidized by GOD to hydrogen peroxidise and coupled with 4 amino-antipyrine (4AAP) and phenol to yield a red quinoneimine dye which is measured at 505nm and indicates concentration of glucose in the sample. HPLC method was used for assessment of HbA1c.

Hemodynamic Measurements

The presence and whole vanishing of the Korotokoff sounds (K1 and K5) was used for the governing the systolic and diastolic blood pressures using an aneroid sphygmomanometer. The mean of 3 supine measurements was used.

Statistical analysis

In present study the complete data are presented in the form of as mean, standard deviation (SD). Baseline readings of two groups of treatment has been compared by applying a paired and unpaired student t-test. The action of both drugs on hemodynamic and metabolic variables has been compared by applying the general linear models and noted that the between-subject variable is β -blocker. Further, the P value < 0.05 was considered significant. The IBM SPSS Statistics version 19.0.0 was used to analyse the data

Ethical Clearance No.:

RESULTS

Age and sex wise distribution

Age and sex wise distribution of the subjects in all two groups under study were assessed. All the two groups consisted of 30 subjects each. Group I consisted of 60% male and 40% female patients. Male patients in Group II were 70% and female 30% (Table 1).

HbA_{1c} assessment

After three month of treatment, a statistically significant decrease in HbA_{1c} levels in Group I (metoprolol) and Group II (nebivolol) was seen as compared to baseline using paired t test. However, the mean difference of nebivolol (0.7) was found to be more than metoprolol (0.5) (Table 2). Furthermore statistically significant decrease in HbA_{1c} level was shown by nebivolol as compared to metoprolol by using unpaired 't' test in both groups (Table 3).

Fasting blood glucose assessment

A statistically significant decrease in fasting blood glucose levels were shown in Group I (metoprolol) and Group II (nebivolol) as compared to baseline using paired t test after three month of treatment. However, the mean difference of nebivolol (8.2) was found to be more than metoprolol (7.5) (Table 4). Furthermore statistically significant decrease in fasting blood glucose level was shown by nebivolol as compared to metoprolol by using unpaired t test in both groups (Table 5).

Postprandial blood sugar assessment

After three month treatment, a statistically significant decrease in postprandial blood glucose levels were shown in Group I (metoprolol) and Group II (nebivolol) as compared to baseline using paired t test. However, the mean difference of nebivolol (20) was found to be more than metoprolol (15.2) (Table 6). Furthermore statistically significant (p value=0.0155) decrease in postprandial blood glucose level was shown by nebivolol as compared to metoprolol by using unpaired t test in both groups (Table 7).

Systolic blood pressure assessment

Systolic blood pressure was significantly decrease in Group I (metoprolol) and Group II (nebivolol) as compared to baseline using paired t test after three month treatment. The mean difference of nebivolol (14.1) was found to be more than metoprolol (13.1) (Table 8). Furthermore statistically significant (p value=0.0355) decrease in systolic blood pressure was shown by nebivolol as compared to metoprolol by using unpaired 't' test in both groups (Table 9).

Diastolic blood pressure assessment

Diastolic blood pressure was significantly decrease in Group I (metoprolol) and Group II (nebivolol) as compared to baseline using paired t test after three month treatment. The mean difference of nebivolol (9.77) was found to be more than metoprolol (7.93) (Table 10). Furthermore statistically significant (p value=0.8147) decrease was not found in diastolic blood pressure by nebivolol as compared to metoprolol by using unpaired t test in both groups (Table 11).

Adverse drug reaction

No any serious adverse drug reaction was shown in nebivolol group but metoprolol group shown fatigue in one patient (table 12).

DISCUSSION

This study was a comparative and observational to evaluate the antihypertensive, metabolic and safety parameters of nebivolol and metoprolol in hypertensive patients co-existing with DM. Cardiovascular risks increased up to two third when the hypertensive person is suffering along with type II diabetes mellitus.²¹ Mostly antihypertensive therapies worsen glucose control and increases complications which are yet to be unclear.²² Since a decade, The benefit of blood pressure lowering may be negated because some antihypertensives may have untoward metabolic effects.²³

The effects of antihypertensive therapy provided by different classes of drugs may differ on glucose metabolism and lipid metabolism, suggests research.²⁴ Increase in sugar in blood while on regimen of antihypertensive it is noted that a forecaster of cardiovascular diseases.²⁵ Insulin resistance constantly pointed for its linking for the endothelial dysfunction which further leads to cardiovascular complications.²⁶ so, above studies indicates a inter link between cardiovascular diseases and metabolic complications.²⁷ Concurrently to this text, necessary to select the antihypertensive drugs with minimum adverse metabolic effects, especially in patients having diabetes mellitus. Despite these drawbacks, there is still room for improvement in clinical outcomes.

Metabolic complications are increased and confirmed in clinical trials while using β -blockers to treat hypertensive patient with co existing diabetes mellitus.²⁸

These β -blockers disturbs insulin release, gluconeogenesis, glycogenolysis and insulin mediated activation of glucose uptake along with weight gain. Nebivolol is highly β_1 -selective drug with vasodilatory properties along with, positive actions on metabolic parameters.²⁹ The clinical study demonstrated that when nebivolol was administered that effectively lowered BP and produced improvement in metabolic parameters like fasting glucose and lipid profile,

and reduced glycosylated haemoglobin (HbA1c).³⁰ Our study was also concluded that diabetic patients with BP exhibited developments in metabolic parameters. With the similar line of research nebivolol shown the similar results in our study i.e. reduces fasting and postprandial sugar level. Significant reduction in fasting blood glucose level is seen in our study from baseline value of 138.4 to 124.4, similarly postprandial blood glucose level is also significant is reduced from baseline value of 203.2 to 183.1 after 3 month of treatment of nebivolol,

Several studies and trials, were conducted using nebivolol (once daily) in patients with mild to moderate essential hypertension, showed a significant reduction in hypertension³¹ and further all these studies were consistence with our study which showed baseline changed by nebivolol from 143.1/98.97 to end point of 128.7/89.20 as compared to metoprolol after 3 months of treatment.

Previous study investigated the metabolic effects of treatment with nebivolol showed that reduction of mean HbA1c from baseline value after treatment. Our study showed similar reduction of HbA1c from baseline value of 7.68 to 6.93 after 12 weeks of treatment of nebivolol.

Notwithstanding being a selective drug for β_1 -adrenoceptors, metoprolol evidence suggests that adverse effects on both carbohydrate and as well as on insulin sensitivity. There has been a significant difference in the characteristics of nebivolol compared to other third-generation β -blockers, such as celiprolol and carvedilol, in most clinical studies.³²

Due to reduction in oxidative stress by nebivolol it showed diverse effects on metabolic processes of body. Further this drug also possesses vasodilatory property to produce antihypertensive action similar to other third generation β -blockers. By above mentioned valuable factors of nebivolol is initially evaluated preclinical models³³ and afterwards established same in humans followed by patients with essential hypertension.³⁴ Mechanistically beta-adrenoceptor antagonism is mediated endothelium-dependent arterial and venous dilatation via the L-arginine-nitric oxide (NO)-dependent pathway³⁵ whereas other third-generation β -blockers mediated vasodilator effect through beta-adrenoceptor antagonism..

CONCLUSION

Nebivolol has shown beneficial effects on glucose metabolism by reducing fasting, postprandial blood sugar and HbA1c level along with beneficial effects on hypertension. nebivolol is a well tolerated β -blocker than metoprolol. It may therefore be recommended as first-line treatment option for the management of patients with type II DM with mild to moderate hypertension.

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Conflict of interest: NIL

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004; 27(5): 1047–1053
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993; 16(2): 434–444.
3. Sarwar N, Gao P, Seshasai SR. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010; 375(9733): 2215–2222.
4. Hu G, Jousilahti P, Tuomilehto J. Joint effects of history of hypertension at baseline and Type 2 diabetes at baseline and during follow-up on the risk of coronary heart disease. *Eur. Heart J*. 2007; 28(24): 3059–3066.
5. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; 365:217-223.
6. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Management Of Arterial Hypertension Of The European Society Of Hypertension; European Society Of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension(ESH) and of the European Society of Cardiology(ESC). *J Hypertens* 2007; 25: 1105-1187.
7. European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21: 1011-1053.
8. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwaniap; American Diabetes Association; American College Of Cardiology Foundation; American Heart Association. Intensive glycaemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation* 2009; 119: 351-357.
9. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; 366: 1545-1553.
10. Williams B, Poulter NR, Brown MJ, Davis M, Mcinnes GT, Potter JF, Sever PS, Thom SM; Bhs Guidelines Working Party, For The British Hypertension Society. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *Br Med J* 2004; 328: 634-640.
11. Roberts WC, Black HR, Bakris GL, Mason RP, Giles TD, Sulkes DJ. The editor's roundtable: revisiting the role of beta blockers in hypertension. *Am J Cardiol* 2007; 100: 253-267.

12. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JTJR, Oakes R, Lukas MA, Anderson KM, Bell DS; Gemini Investigators. Metabolic effects of carvedilol vs metoprolol in-patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; 292: 2227-2236.
13. Baldwin CM, Keam SJ. Nebivolol: in the treatment of hypertension in the US. *Am J Cardiovascular Drugs* 2009; 9: 253-260.
14. Wilkinson IB, Qasem A, McEniery CM, Webb DJ, Avolio AP, Cockcroft JR. Nitric oxide regulates local arterial distensibility in vivo. *Circulation*. 2002 Jan 15; 105(2):213-7.
15. Schmitt M, Avolio A, Qasem A, McEniery CM, Butlin M, Wilkinson IB, Cockcroft JR. Basal NO locally modulates human iliac artery function in vivo. *Hypertension*. 2005 Jul; 46(1):227-31.
16. Cockcroft JR, Chowienzyk PJ, Brett SE, Chen CP, Dupont AG, Van NL, Wooding SJ, Ritter JM. Nebivolol vasodilates human forearm vasculature: evidence for an l-arginine/NO-dependent mechanism. *J Pharmacol Exp Ther*. 1995;274:1067-1071.
17. Broeders MA, Doevedans PA, Bekkers BC, Bronsaer R, van GE, Heemskerk JW, Egbrink MG, van BE, Reneman RS, Van Der ZR. Nebivolol: a third-generation -blocker that augments vascular nitric oxide release: endothelial (2)-adrenergic receptor-mediated nitric oxide production. *Circulation*. 2000;102:677-684
18. Bouchie JL, Hansen H, Feener EP. Natriuretic factors and nitric oxide suppress plasminogen activator inhibitor-1 expression in vascular smooth muscle cells. Role of cGMP in the regulation of the plasminogen system. *Arterioscler Thromb Vasc Biol*. 1998;18:1771-1779.
19. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation*. 2006;113:1888-1904
20. Bortel LM, Efficacy, tolerability and safety of nebivolol in patients with hypertension and diabetes: a post-marketing surveillance study. *European Review for Medical and Pharmacological Sciences*. 2010; 14: 749-758
21. Bakris G, Vassalotti J, Ritz E, Wanner C, Stergiou G, Molitch M, Nesto R, Kaysen GA, Sowers JR; CKD Consensus Working Group. National Kidney Foundation consensus conference on cardiovascular and kidney diseases and diabetes risk: an integrated therapeutic approach to reduce events. *Kidney Int*. 2010;78:726-36.
22. Bakris GL, Sowers JR, Glies TD, Black HR, Izzo JLJR, Materson BJ, Oparil S, Weber MA. Treatment of hypertension in patients with diabetes--an update. *J Am Soc*
24. *Hypertens*. 2010;4:62-7.
25. Karnes JH, Cooper-DeHoff RM. Antihypertensive medications: benefits of blood pressure lowering and hazards of metabolic effects. *Expert Rev Cardiovasc Ther*. 2009 Jun;7(6):689-702.
26. Gorre F, Vandekerckhove H. Beta-blockers: focus on mechanism of action. Which beta-blocker, when and why? *Acta Cardiol*. 2010 Oct;65(5):565-70.
27. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. *Lancet*. 2012 Aug 11;380(9841):601-10
28. Bagul PK, Banerjee SK. Insulin resistance, oxidative stress and cardiovascular complications: role of sirtuins. *Curr Pharm Des*. 2013;19(32):5663-77
29. Ripley TL, Saseen JJ. β -blockers: a review of their pharmacological and physiological diversity in hypertension. *Ann Pharmacother*. 2014 Jun;48(6):723-33.
30. Tsujimoto T, Sugiyama T, Shapiro MF, Noda M, Kajio H. Risk of Cardiovascular Events in Patients With Diabetes Mellitus on β -Blockers. *Hypertension*. 2017 Jul;70(1):103-110
31. Marketou M, Gupta Y, Jain S, Vardas P. Differential metabolic effects of beta-blockers: an updated systematic review of nebivolol. *Curr Hypertens Rep*. 2017; 19: 22.
32. Olawi N, Krüger M, Grimm D, Infanger M, Wehland M. Nebivolol in the treatment of arterial hypertension. *Basic Clin Pharmacol Toxicol*. 2019 Sep;125(3):189-201
33. Silva IVG, De Figueiredo RC, Rios DRA. Effect of Different Classes of Antihypertensive Drugs on Endothelial Function and Inflammation. *Int J Mol Sci*. 2019 Jul 14;20(14):3458
34. Ozyıldız AG, Eroglu S, Bal U, Atar I, Okayay K, Muderrisoglu H. Effects of Carvedilol Compared to Nebivolol on Insulin Resistance and Lipid Profile in Patients With Essential Hypertension. *J Cardiovasc Pharmacol Ther*. 2017 Jan;22(1):65-70.
35. Atwa A, Hegazy R, Mohsen R, Yassin N, Kenawy S. Protective Effects of the Third Generation Vasodilatory Beta - Blocker Nebivolol against D-Galactosamine - Induced Hepatorenal Syndrome in Rats. *Open Access Maced J Med Sci*. 2017 Dec 13;5(7):880-892.
36. Shin, Choi J, Hong YJ, Geu-Ru J, Dong W, Kim, Dae-Hyeok K, Mancía YY, Manolis G, Athanasios J. Yoon, Hyuck-Jun P, Sang Won Real-world efficacy and safety of nebivolol in Korean patients with hypertension from the benefit Korea study. *J Hypertens*.: March 2020; 38(3): 527-535.
37. Kawaguchi S, Okada M, Ijiri E, Koga D, Watanabe T, Hayashi K, Kashiwagi Y, Fujita S, Hasebe N. β_3 -Adrenergic receptor blockade reduces mortality in endotoxin-induced heart failure by suppressing induced nitric oxide synthase and saving cardiac metabolism. *Am J Physiol Heart Circ Physiol*. 2020 Feb 1; 318(2): H283-H294.